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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/597,580	06/20/2000	Gary L. Griffiths	018733/0987	5842

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EXAMINER
JONES, DAMERON L

ART UNIT	PAPER NUMBER
1616	28

DATE MAILED: 07/02/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/597,580	GRIFFITHS ET AL.	
	Examiner	Art Unit	
	D. L. Jones	1616	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-42,44 and 46-54* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16, 18, 20-42, 44, 46, and 50-54* is/are rejected.

7)☒ Claim(s) *17,19 and 47-49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 25 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

ACKNOWLEDGMENTS

1. The Examiner acknowledges receipt of the preliminary amendment filed 3/24/03, Paper No. 24. Likewise, the Examiner acknowledges the acceptable request for continuing examination (RCE) of the instant application.

Note: Claims 1-42, 44, and 46-54 are pending.

112 REJECTIONS

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claim 1 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In order to clarify the record, Applicant is respectfully requested to respond to the following. Claim 1 (section A): Is this how Applicant's invention should be interpreted? The composition comprises one of the following: (1) a therapeutic naked antibody or (2) a first conjugate comprising a targeting moiety and a first therapeutic agent. If not, Applicant is respectfully requested to amend the claims to clearly indicate what is being claimed.

Claim 1 (section C): Is this how Applicant's invention should be interpreted? The composition comprises one of the following: (1) a second therapeutic agent or (2) a

second conjugate having a low molecular weight hapen. If not, Applicant is respectfully requested to amend the claims to clearly indicate what is being claimed.

103 REJECTIONS

4. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 1-16, 18, 20-38, 40-42, 46, and 50-54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gustavson et al (US Patent No. 5,420,105) in view of Gustavson et al (US Patent No. 5,283,342) in further view of Maddock (US Patent No. 5,474,772).

Gustavson et al (US Patent No. 5,420,105) disclose polymeric carriers that may be attached to antibodies to form immunoconjugates that deliver a drug to target cells (e.g., tumor cells) in vivo. The polymeric carrier may be attached to a proteinaceous or a non-proteinaceous ligand or anti-ligand to form a conjugate (see entire document, especially, abstract; column 3, lines 1-13; column 4, lines 11-20; column 4, lines 47-51; column 5, lines 11-17; column 14, lines 16-42; column 15, lines 58-64). Figure 1 discloses a schematic (Scheme 3) wherein a targeting moiety, anti-ligand, ligand, and ligand-active agent are utilized. The polymeric carrier may comprise one or more multiple drug-binding domains (column 3, lines 62-63). The ligand/anti-ligand pair is a

complementary/anti-complementary set of molecules (e.g., zinc finger protein/double stranded DNA fragment, hapten/antibody, lectin/carbohydrate, ligand/receptor, and biotin/avidin) [column 4, lines 21-28]. The anti-ligand has high affinity and is preferably has multivalent binding with the complementary ligand. The anti-ligand may be galactose residues (column 4, lines 29-39). Table I, column 7, discloses doxorubicin as a possible drug for use in the Gustavson et al invention. The proteinaceous targeting moieties include antibodies, antibody fragments, serum proteins, enzymes, peptide hormones (e.g., follicle stimulating hormone), and biologic response modifies which may be lymphokines (columns 14-15, bridging paragraph; column 15, lines 19-30). The anti-ligand is administered as the clearing agent (column 17, lines 67-68). In column 18, lines 6-25, Gustavson et al disclose a ligand-polymeric carrier-drug composition. In Example 1, columns 19-20, Gustavson et al disclose a drug adriamycin (doxorubicin) which is bound to a polymeric carrier (see also, column 23, Example 5). In columns 21-22, Example 3, Gustavson et al disclose a polymeric-carrier-antibody conjugate. In columns 23-25, Example 6, the preparation of a polymeric carrier-streptavidin conjugate is disclosed. In columns 30-31, Examples 9-11, Gustavson et al disclose compositions wherein subjects having cancer are administered an antibody composition.

However, Gustavson et al fail to disclose render obvious the incorporation of various radionuclides (therapeutic agents), cytokines, drugs, toxins, and ligands. Specifically, in regards to independent claim 1, the references fails to clearly set forth what is encompassed in their definition of and ligand-active cite such that one can state without any doubt that such term encompasses radionuclides, drugs, and toxins.

Gustavson et al (US Patent No. 5,283,342) disclose compositions that may be used for therapeutic purposes. The compositions comprise a targeting moiety that is conjugated to one member of a ligand/anti-ligand pair (see entire document, especially, abstract; column 1, lines 6-12; column 1, line 36 – column 2, line 1; column 5, lines 27-37). The therapeutic drugs may be administered alone or as targeted conjugates (column 2, lines 48-50). The therapeutic agent comprises a targeting moiety that subsequently comes in contain with a rapidly clearing diagnostic or therapeutic agent (column 3, lines 1-59; column 4, lines 1-11). An observed phenomenon of Gustavson et al is that the multivalent anti-ligand crosslinks targeting moiety-ligand conjugates on a cell surface. The conjugation on the cell surface initiates of facilitates internalization of the result complex. Likewise, Gustavson et al discloses that the apparent loss of targeting moiety-ligand from the cell may very well may result from internal degradation of the conjugate and/or release of active agent from the conjugate (column 5, lines 1-12). The targeting cell population may be tumor cells. Thus, possible targeting moieties include antibodies, peptides, and hormones (column 6, lines 13-26). Possible active agents include toxins, drugs, and radionuclides (column 6, lines 27-28). Preferred toxins include abrin, ricin, modeccin, Pseudomonas exotoxin A, Diphtheria toxin, pertussis toxin, and Shiga toxin (column 6, lines 40-52). Possible drugs include doxorubicin, methotrexate, 5-fluorouracil, mercaptopurine, bromodeoxyuridine, iododeoxyuridine, a nitrosourea compound, mercaptoethane sulfonate, taxol, cyclocytidine, dihydro-5-azacytidine, 4'-deoxy-doxorubicin, and dideoxycitidine (column 6, lines 53-62; columns 6-7, bridging paragraph). Possible radionuclides include

gamma-, positron-, Auger electron-, X-ray-, and fluorescence-emitters with the preferred radionuclides being useful for therapeutic purposes (column 7, lines 29-44). Possible ligands include biotin, haptens, and epitopes (column 7, lines 45-52).

Maddock disclose the therapeutic treatment of a patient with a medically useful agent that may be radiolabel and irradiated to destroy tumor cells or prevent the growth of the tumors (see entire document, especially, abstract; column 5, lines 17-25). The radiolabeled material may be an anti-tumor monoclonal antibody (column 5, lines 40-41; column 7, lines 38-44). The medical agent may be labeled with a hapten, hapten-antibody, enzymes, toxins, drugs, or radioemitting elements (column 7, lines 58-60; column 8, lines 3-5 and 33-43).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the invention of Gustavson et al (US Patent No. 5,420,105) using the teachings of Gustavson et al (US Patent No. 5,283,342) and Maddock and generate compositions as set forth in independent claims 1, 37, and 38 wherein various radionuclides, cytokines, drugs, toxins, and ligands are utilized for the following reasons. (1) While the primary reference (Gustavson et al, US Patent No. 5,420,105) does not set forth a specific definition all that is encompassed in their definition of an ligand-active agent (see Figure 1, Scheme 3, and column 3, lines 5-13), the secondary reference (Gustavson et al, US Patent No. 5,283,342), column 1, lines 59-65, discloses that the active agent is a diagnostic or therapeutic agent which includes radionuclides, drugs, and toxins. Hence, components A – C of Applicant's independent claim 1 are obvious.

(2) The primary reference renders its obvious to add a therapeutic agent (e.g., radionuclide, see column 17, lines 27-45, especially, lines 39-43) because Gustavson et al disclose that elevated doses of their composition may be used when pretargeting procedures are conducted because of the decoupling of a targeting moiety localization and radionuclide localization. Hence, the skilled practitioner in the art would recognize that the presence of a radionuclide is possible.

(3) Both Maddock and the secondary reference disclose that cytokines are useful in compositions having the limitations of independent claims 1, 37, and 38. For example, see column 14, lines 60-65.

(4) The secondary reference discloses various toxins and drugs that are encompassed in the instant invention (see the specific one disclosed above).

(5) The secondary reference discloses various useful radionuclides useful in combination with compositions of the primary reference (see the specific ones disclosed above).

(6) The secondary reference discloses various suitable ligands in combination with compositions of the primary reference (see the specific ones disclosed above).

(7) Maddox discloses that it is well known in the art to label medically useful agents with enzymes, toxins, drugs, or radioemitting elements. In addition, the reference discloses that it is known in the art to use medically useful agents in combination with drugs, drug/hapten complexes, enzymes, carbohydrates, antibodies, cytokines, glycoproteins, biological response modifiers, lipids/glycolipids, proteolipids, hormones, and proteins.

Since all of the references are directed to medically useful compositions that may comprise a targeting agent (e.g., an antibody) in combination with a ligand, and/or a therapeutic agent, the references may be considered to be within the same field of endeavor. Thus, the references are combinable.

6. Claims 37-39 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gustavson et al (US Patent No. 5,420,105).

Gustavson et al (see discussion above) fail to specifically state that a radionuclide may be present. However, it would be obvious to one of ordinary skill in the art at the time the invention was made to incorporate a radionuclide because the that elevated doses of their composition may be used when pretargeting procedures are conducted because of the decoupling of a targeting moiety localization and radionuclide localization. Hence, the skilled practitioner in the art would recognize that you may have a radionuclide present.

CLAIM OBJECTIONS

7. Claims 17, 19, and 47-49 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Note: The claims are distinguished over the prior art because the prior art neither anticipates nor renders obvious the limitations of the dependent claims in combination with those of their respective intervening claims.

8. Any inquiry concerning this communication or earlier communications from the examiner should be directed to D. L. Jones whose telephone number is (703) 308-4640. The examiner can normally be reached on Mon.-Fri. (alternate Mon.), 6:45 a.m. - 4:15 p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Thurman Page can be reached on (703) 308 - 2927. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4556 for regular communications and (703) 308-4556 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

D. L. Jones
Primary Examiner
Art Unit 1616

June 26, 2003